REMARKS

Status of the Claims

Claims 4, 5, 30, 31, and 33 have been canceled without prejudice to or disclaimer of the subject matter therein. Claims 6, 10, 11, 13, 19, 20, 27 and 32 have been amended without prejudice to or disclaimer of the subject matter therein, as described elsewhere herein. Support for the amendments and new claims can be found in the original claims or in the specification, as described herein below. Therefore, no new matter has been added by amendment.

Claims 1-3, 6, 10, 11, 13-16, 19, 20, 23, 27, 28, and 32 are now pending. The Examiner's comments are addressed below in the order set forth in the Office Action.

March 15, 2004 Telephonic Interview

On March 15, 2004, the undersigned discussed the rejection of claims 1-6, 10, 11, 13-16, 19, 20, 23, 27, and 28 under 35 U.S.C. § 101 with the Examiner. In particular, acceptable forms of additional evidence to respond to the Section 101 rejection, including a multi-species MLH1 sequence alignment, were discussed. Applicant's representative wishes to thank the Examiner for the helpful suggestion.

Objection to the Claims

Claims 10, 11, 13, 19, 20 and 27 are objected to because they recite the term "a." Per the Examiner's suggestion, the claims have been amended to recite "the," thereby obviating the objection.

The Rejections of the Claims under 35 U.S.C. § 101 Should Be Withdrawn

The rejection of claims 1-6, 10, 11, 13-16, 19, 20, 23, 27, and 28 under 35 U.S.C. § 101 has been maintained. The Office Action states that the function, and thus the utility, of the claimed invention is based upon homology to the *Arabidopsis* MLH1 isolated by Jean *et al.* and that this evidence insufficient. The rejection is respectfully traversed.

Applicants note that one piece of evidence for the utility of the claimed invention is the homology between the *Arabidopsis* MLH1 sequence and Applicant's rice MLH1 sequence. Specifically, the *Arabidopsis* MLH1molecule and Applicant's rice MLH1 molecule share 74.4% similarity and 66.6% identity at the amino acid level; 67.9% identity at the nucleic acid level. See the specification, Figures 3 and 4. However, this is not the only evidence Applicant has disclosed: Figure 2 sets forth a region of homology with the yeast MutL signature sequence in bold. MLH1/MutL sequences are highly conserved across distantly related organisms. Consequently, the art worker would find the combination of (1) robust homology between a known MLH1/MutL molecule and Applicant's MLH1molecule and (2) the presence of a MutL signature sequence in Applicant's molecule to be strong evidence for the asserted utility.

At the Examiner's suggestion, Applicant has prepared a multi-species sequence alignment of MLH1/MutL orthologs generated with the PileUp algorithm that illustrates the strong homology between Applicant's rice MLH1 and the MLH1/MutL sequences of other organisms. See **Tab 1**. In particular, the amino acid sequences of human, rat, *Arabidopsis*, yeast, and *E. coli* MLH1/MutL orthologs are aligned with Applicant's rice MLH1 amino acid sequence (SEQ ID NO:2, in bold-face). Identical residues are shaded in medium gray; similar residues are shaded in light and dark gray. The MutL/PMS1 signature sequence of Figure 2 is also shown in the alignment (single underline). In addition, the alignment sets forth the PFAM DNA-mis-repair domain made of record as Exhibit A in the previous response filed May 19, 2003 (double underline).

The identification of the PFAM DNA-mis-repair family domain in SEQ ID NO:2 was accomplished by searching the entire amino acid sequence of SEQ ID NO:2 against the PFAM database. The PFAM database provides a curated collection containing over 7316 well-characterized protein family domains with high quality alignments and functional domains. PFAM families are built upon a seed alignment, a hand edited multiple alignment representing the family. From the seed alignment, a Hidden Markov Model is constructed, which can be used to identify new members of the family. See, e.g., Sonhammer *et al.* (1997) *Proteins* 28(3):405-420 and the PFAM home page at http://www.sanger.ac.uk/Software/Pfam/help/faq.shtml. The PFAM DNA-mis-repair family is built upon a 28-member seed alignment, with over 160 total

family members. The Office Action correctly points out that this conserved domain lies beyond the conserved N-terminal region shown in Figure 2. However, this does not diminish the relevance of the PFAM evidence. Rather, the presence of a PFAM DNA mismatch repair domain consensus sequence in SEQ ID NO:2 constitutes additional, strong scientific evidence that Applicant's molecule functions as a MLH1 protein.

Applicant has also performed a comparison of SEQ ID NO:2 against the InterPro Database available at the EMBL-EBI European Bioinformatics Institute website at http://www.ebi.ac.uk/InterProScan/. This database also identifies a DNA mismatch repair conserved domain in SEQ ID NO:2. See **Tab 2**. Applicant emphasizes that the InterPro Database entry for mismatch repair proteins was created October 8, 1999. This supports a conclusion that, even at the time Applicant filed the present application, the consensus domain for the mismatch repair family was recognized in the art and one of skill in the art would not have doubted that Applicant's molecule functions as a MLH1 protein.

Finally, Applicant submits herewith the results of a recent BLAST search setting forth an alignment between SEQ ID NO:2 and Accession No. AP003238, a rice MLH1 homolog. AP003238 possesses over 99% identity with SEQ ID NO:2 (**Tab 3**).

Turning to the issues raised in the present rejection, the Office Action reiterates that Jean *et al.* indicated that mutant studies were required to definitively prove that their *Arabidopsis* MLH1 molecule played a role in mismatch repair. Based upon this statement, the Office Action asserts that Applicant must demonstrate additional experimental results to demonstrate utility for the rice MLH1 molecule. Applicant disagrees for the reasons stated in the following paragraph.

Section 101 does not require definitive scientific proof to establish utility. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1565, 39 USPQ2d 1895, 1900 (Fed. Cir. 1996)("[A] 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' is sufficient."). The specific quote by Jean *et al.* relied upon by the Office Action is as follows: "Despite obvious similarities between *AtMLH1* and its counterparts in other eukaryotes, *definite proof* that *AtMLH1* plays a role in MMR [mismatch repair] in *Arabidopsis* can only be obtained through mutant analysis." See Jean *et al.* (1999) *Mol. Gen. Genet.* 262:633-642, page 641, 2nd paragraph (emphasis added). It is clear from the context of the quote that Jean *et al.* were

referring to absolute scientific proof of the role played by *AtMLH1*. Applicant emphasizes that definitive scientific proof is not required under Section 101. Given Applicant's original disclosure, one of skill in the art would not doubt the asserted utility of the rice MLH1 molecule.

In the preceding response, Applicant emphasized that Jean *et al.* displayed certainty that their molecule was an MLH1 molecule, even though the mutant studies of Jean *et al.* failed to yield a disrupted *AtMLH1* or any data related to disrupted function. For instance, Jean *et al.* titled their journal article "Isolation and characterization of *AtMLH1*, a *MutL* homologue from *Arabidopsis thaliana*." In their abstract, Jean *et al.* state "Using degenerate primers, we have cloned the first plant homologue of the *E. coli MutL gene*...." See page 634. Jean *et al.* further state, "In the work reported here, we describe the isolation and initial characterization of the *Arabidopsis MLH1* gene, the first *MutL* homologue identified in plants." See page 634, first paragraph. These statements demonstrate that one of skill in the art would not doubt a functional assignment based upon sequence homology, regardless of whether mutant analysis has been carried out. The Office Action finds this unpersuasive, however, on the ground that "it is not pursuant upon a third party to establish a substantial utility upon Applicant's invention." This statement does not comport with the utility standard.

It is well-established that an Applicant need only assert a utility. *See In re Brana*, 34 U.S.P.Q.2d 1437, 1441 (Fed. Cir. 1995). Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the Applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. *Id.* The inquiry into what the view of one of ordinary skill in the art necessarily requires evidence from third parties. Applicant relies upon the statements of Jean *et al.* not to *demonstrate* their asserted utility, but to show that one of skill in the art would not doubt a functional assignment based upon sequence homology, regardless of whether mutant analysis has been carried out.

The Office Action also asserts that little is known about the mismatch repair system in plants, relying upon a statement in Jean *et al.* Jean *et al.* was published in 1999 and this statement is mainly relevant to the knowledge regarding mismatch repair genes of plants at that time. However, the statement in no way reflects the knowledge in the art regarding the mismatch

repair system in eukaryotes. In fact, the paragraph preceding the passage relied on in the Office Action, Jean *et al.* recognized that "the components of the DNA mismatch repair apparatus of prokaryotes, yeast, and mammals have been isolated and characterized in great detail." Jean *et al.* page 612, paragraph 1. As Applicant has shown in the preceding paragraphs, the MLH1 sequences of widely divergent organisms have substantial conserved regions and significant homology exists between the rice MLH1 sequence and the MLH1 sequences of other organisms. Given the highly conserved nature of the MLH1 sequences, one of skill in the art would not have doubted that Applicant's molecule functions as a MLH1 protein.

By way of analogy, Applicant notes that four *Arabidopsis* mismatch repair MSH proteins (*AtMSH2*, *AtMSH3*, *AtMSH6-1*, and *AtMSH6-2*) were identified based upon their relationship with MSH genes from other species. Ade *et al.* (1999) *Mol. Gen. Genet.* 262:239-249, 246, first full paragraph (**Tab 4**). Although mutagenesis studies were not carried out, the homology based assignment of these proteins as MSH proteins was accepted by those of skill in the art and published in a peer-reviewed journal. Recently, the results of TDNA mutant and RNAi studies using *AtMSH2* were published, demonstrating that the *AtMSH2* gene did function in the mismatch repair system, as evidenced by the reduction of stability of genomic and transgenic microsatellite sequences in plant lines bearing inactivated MSH genes. Leonard *et al.* (2003) *Plant Physiology* 133:328-338 (**Tab 5**). Leonard *et al.* conclude that this evidence has "directly implicated plant MSH proteins- and by extension MLH proteins—in maintenance of plant genomic stability." Leonard *et al.* page 334, column 2, first full paragraph. Applicant emphasizes that Leonard *et al.* demonstrates the following two points: First, that those of skill in the art find homology-based identification sufficient to justify committing substantial resources to using mutated MSH2 in the expectation that genetically unstable plant lines will be generated and, second, that the mutant studies exactly confirm the earlier asserted homology-based function of Ade *et al.*

Thus, one of skill in the art would not doubt that Applicant's molecule functions as a MLH1 protein. Accordingly, the rejection of claims 1-3, 6, 10, 11, 13-16, 19, 20, 23, 27, 28, and 32 should be withdrawn, accordingly.

The Rejections of the Claims under 35 U.S.C. § 112, First Paragraph Should Be Withdrawn

Claims 1-6, 10, 11, 13-16, 19, 20, 23, 27, 28, and 30-33 remain rejected under 35 U.S.C. § 112, first paragraph, enablement. The rejection of these claims is respectfully traversed.

As an initial matter, Applicant notes that claims 4, 5, 30, 31, and 33 have been canceled without prejudice or disclaimer of the subject matter therein. Accordingly, the rejection is obviated to the extent it is directed to nucleic acid molecules that comprise fragments of SEQ ID NOS:1 or 2, or nucleic acid molecules with 85 to 90% identity to SEQ ID NOS:1 or 2, or molecules that would hybridize to SEQ ID NO:1.

The Office Action asserts that one of skill in the art would not be able to use the present invention on the grounds that utility has not been established. For the reasons stated above, one of skill in the art would not doubt that Applicant's molecule functions as a MLH1 protein given the highly conserved nature of the mismatch repair proteins, including MLH1 sequences and the existence of MLH1/MutL mismatch repair consensus domains within Applicant's disclosed sequence. Furthermore, one of skill in the art would immediately recognize how to use a newly identified member of the mismatch repair system, as described in the specification.

> The plant cellular mismatch repair system is inhibited through the use of transposon tagging of an MLH1 gene, sense- and antisense- suppression of an MLH1 gene, antibody binding to an MLH1 polypeptide or variant polypeptide, targeted mutagenesis of specific amino acid residues encoded by an MLH1 gene, and competition with a mismatch repair impaired MLH1 polypeptide through transgenic over-expression of the impaired polypeptide.

See the specification on page 4, lines 19-24. See also Leonard *et al.*, in which transposon tagging and RNAi approaches were utilized to generate plant lines with reduced genetic stability. Thus, Applicant's claimed invention satisfies the standards of Sections 101 and 112 as expressed by the Federal Circuit. *In re Brana*, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995)(overturning the PTO's Section 112 rejection on the grounds that an incorrectly rigorous standard had been applied).

One of skill in the art would be able to practice the uses identified by Applicant because techniques and methods for the generation of plants with mutated sequences leading to decreased expression are known in the art. See the specification, page 23, line 6, to page 29, line 19 (discussing transposon tagging; antisense and sense cosuppression methods; inhibition of

endogenous MLH1 protein through competition with an exogenous, functionally impaired MLH1 protein; and methods for transient suppression of the plant cellular mismatch repair system) and page 9, lines 2-14 (describing standard mutagenesis techniques). Applicant has also disclosed the MutL signature sequence for the rice *MLH1* sequence, as well as an alignment between the sequences for Applicant's rice *MLH1* sequence and the *Arabidopsis MLH1* sequence. See Figures 2, 3 and 4. By aligning these sequences, one of skill in the art can determine conserved regions likely to be susceptible to mutation or truncation. Art recognized screening assays for mismatch repair are set forth in the specification on page 9, lines 22-26. Based on the guidance regarding the consensus signature sequences of the *MLH1* polypeptide, and the methods for identifying additional residues critical for mismatch repair activity, the skilled artisan could choose among possible modifications to produce polypeptides within the parameters set forth in the claims and then test these modified variants for modified mismatch repair activity.

Applicant emphasizes that it is customary in the art to make a number of sequences and to test them in a large-scale assay to practice the techniques set forth on pages 23-29 of the specification. Because such experiments are routine, they would not be considered "undue experimentation" under *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Thus, the rejection of claims 4 and 5 should be withdrawn and the present rejection should not be applied to new claims 30-33.

In summary, the practice of the claimed subject matter does not require undue experimentation. The present rejection under Section 112, first paragraph, enablement, should be withdrawn and should not be applied to the new claims or the claims as amended.

The Rejections Under 35 U.S.C. § 112, First Paragraph, Written Description, Should be Withdrawn

Claims 30-33 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of an adequate written description. This rejection is respectfully traversed.

As noted above, claims 30, 31, and 33 have been canceled without prejudice or disclaimer of the subject matter therein. Claim 32 has been amended to independent form.

Accordingly, the rejection is obviated to the extent it is directed to nucleic acid molecules that comprise fragments of SEQ ID NOS:1 or 2, or nucleic acid molecules with 85 to 90% identity to SEQ ID NOS:1 or 2, or molecules that would hybridize to SEQ ID NO:1.

The Office Action recites MPEP § 2163 for the principle that a sequence cannot be described solely by function. However, a genus *may* be described by means of a recitation of a representative number of DNAs, defined by nucleotide sequence, falling within the scope of the genus, *or* by means of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1569 (Fed. Cir. 1997); *see also* Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1, "Written Description" Requirement, 66 Fed. Reg. 1099, 1106 (2001). An Applicant may also rely upon functional characteristics in the description, provided there is a correlation between the function and structure of the claimed invention. *Id., citing Lilly* at 1568.

Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. 66 Fed. Reg. 1099, 1106 (2001). Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. 66 Fed. Reg. 1099, 1106 (2001).

Claim 32 meets the standard for written description because it describes the genus claimed in terms of both structure and function. Specifically, claim 32 recites nucleotide sequences having at least 95% sequence identity to the sequence set forth in SEQ ID NO:1 (or the cDNA insert of PTA-2021). Ninety-five percent sequence identity is a *very predictable structure* of the sequences encompassed by the claimed invention. Further, claim 32 specifies that the encoded polypeptide have mismatch repair activity, thereby providing a functional characterization of the sequences claimed in the genus. As discussed above, there is an art-recognized correlation between *MLH1* sequences and the family of mismatch repair enzymes. Given SEQ ID NO:1 as a representative species, the functional characterization of the sequences claimed, and the knowledge and level of skill in the art, a person of ordinary skill could envision

the claimed invention, *i.e.*, a sequence having at least 95% sequence identity to the sequence set forth in SEQ ID NO:1 (or the cDNA insert of PTA-2021).

Applicant emphasizes that Example 14 of the Revised Interim Written Description Guidelines is directed to a generic claim: a protein having at least 95% sequence identity to the sequence of SEQ ID NO:3, wherein the sequence catalyzes the reaction A → B. The Training Materials concludes that the generic claim of Example 14 is sufficiently described under § 112, first paragraph, because 1) "the single sequence disclosed in SEQ ID NO:3 is representative of the genus" and 2) the claim recites a limitation requiring the compound to catalyze the reaction from A → B. The Guidelines conclude that one of skill in art would recognize that the Applicants were in possession of the necessary common attributes possessed by the members of the genus. Consequently, the sequences encompassed by the genus of claim 32 are defined by relevant identifying physical and chemical properties. Therefore, claim 32 satisfies the written description standard.

Accordingly, the rejection of claim 32 under 35 U.S.C. §112, first paragraph, for lack of written description should be withdrawn.

CONCLUSION

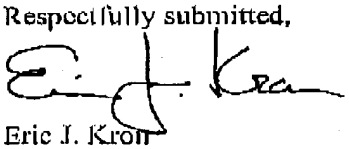
In view of the aforementioned amendments and remarks, Applicants respectfully submit that the rejections of the claims under 35 U.S.C. § 1-3, 6, 10, 11, 13-16, 19, 20, 23, 27, 28, and 32 are overcome. The Examiner is respectfully requested to withdraw the rejections and allow claims 1-3, 6, 10, 11, 13-16, 19, 20, 23, 27, 28, and 32. In any event, the Examiner is respectfully requested to enter the above amendments for purposes of further prosecution. The amendments were not made earlier because the amendments were made in response to the Examiner's suggestion.

Accordingly, in view of the above remarks, it is submitted that this application is now in condition for allowance. Early notice to this effect is solicited.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,



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